



# COVID Vaccines: Approaches to vaccine trial design

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November 4, 2020

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These are my views, and do not represent those of the NIH, DHHS, or the US government.

# Plan

- Vaccine research
- Ethical challenges in vaccine trials
- Approaches to testing a SARS CoV-2/COVID-19 vaccine
- Current status/ COVID-19 vaccine landscape

# Vaccines

- “With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction...”
- Since 2000-
  - Deaths in children < 5yo reduced (Millennium Development Goals)
  - More children reached than ever before (>100 million in 2005-07)
  - More vaccines available and more lives saved in developing countries
  - More money available through innovative funding mechanisms
  - Most productive decade in history of vaccine development
  - Global vaccine market has tripled, vaccine industry one of fastest growing sectors of industry

WHO, UNICEF, and the World Bank. State of the world's vaccines and immunization, 3<sup>rd</sup> Ed. Geneva, WHO, 2009

TABLE 1. CURRENTLY LICENSED VACCINES

Adenovirus	Meningococcal B
Anthrax	Mumps
Cholera	Pertussis
Dengue	Pneumococcal conjugate
Diphtheria	Pneumococcal polysaccharide
Enterovirus 71	Polio, inactivated
Hemophilus influenzae type b	Polio, live
Hepatitis A	Rabies
Hepatitis B	Rotavirus
Human papilloma virus	Rubella
Influenza, live	Smallpox
Influenza, killed	Tetanus
Japanese encephalitis	Tick-borne Encephalitis
Malaria RTS/S	Varicella
Measles	Yellow fever
Meningococcal A, C, W, Y	Zoster

Plotkin S. Vaccines we Need but Don't Have.

*Viral Immunology* 2018

TABLE 2. SELECTED DISEASES AND INFECTIONS FOR WHICH WE DO NOT HAVE LICENSED VACCINES OR ONLY PARTIALLY EFFECTIVE VACCINES

Campylobacter	Human immunodeficiency virus
Candida	Influenza, avian
Chikungunya	Influenza, conserved
Chlamydia	Leishmaniasis
Clostridium difficile	Lyme disease
Cryptosporidium	Malaria
Cytomegalovirus	Metapneumovirus
Ebola	Norovirus
Epstein-Barr virus	Parainfluenza
Escherichia coli, toxin producing	Respiratory syncytial virus
Escherichia coli, urine tract	Salmonella paratyphi A
Helicobacter pylori	SARS
Hemophilus influenzae, nontypable+Moraxella for otitis	Shigella
Hepatitis C	Staphylococcus
Hepatitis E	Strep Group A
Herpesvirus 6	Strep Group B
Herpes simplex	Trypanosomiasis
	Tuberculosis
	West Nile

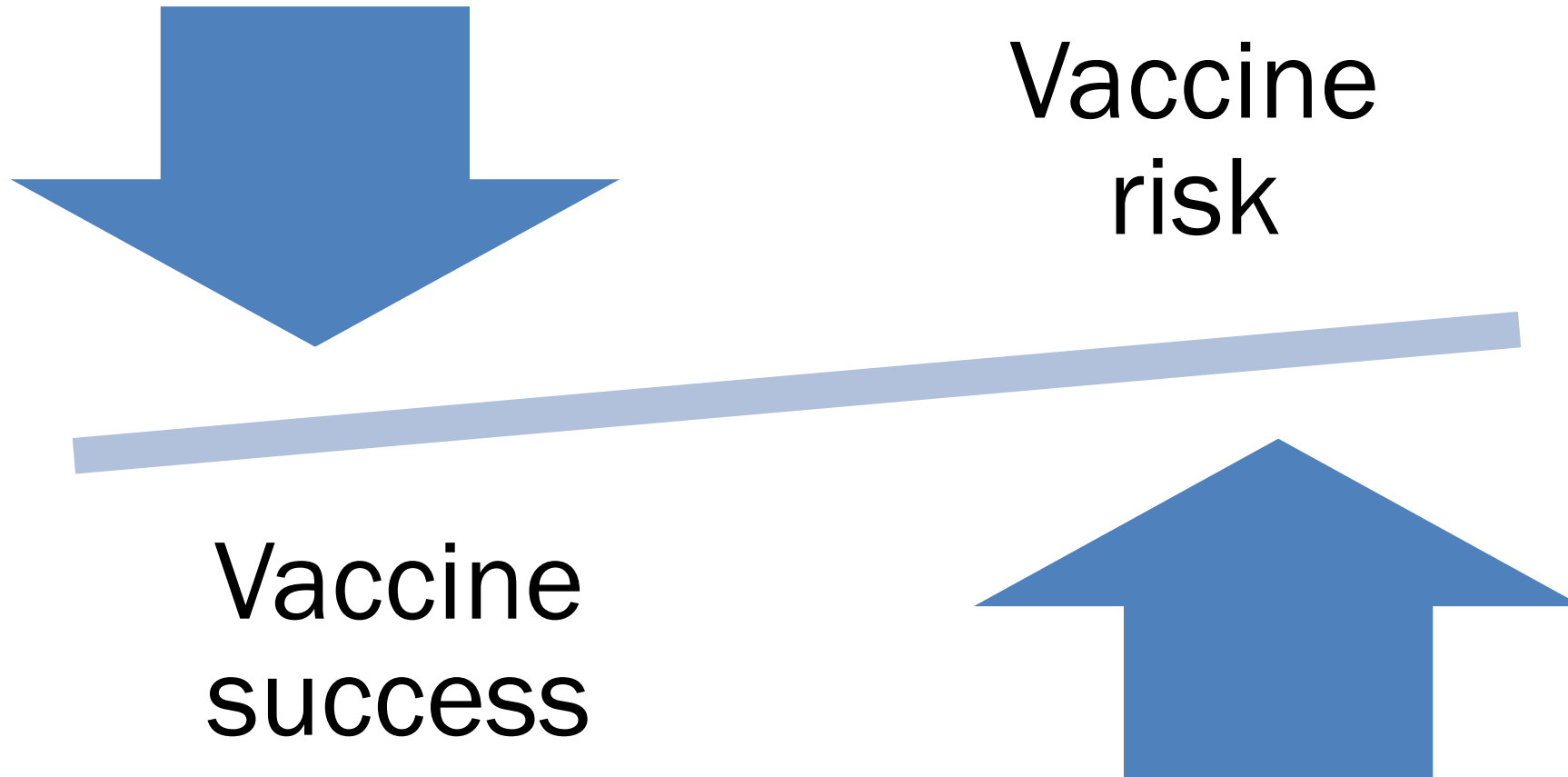
SARS, severe acute respiratory syndrome.

One of the brightest chapters in the history of science is the impact of vaccines on human longevity and health.” (S Plotkin, 2014

# Vaccines

- Substantial contributions to global public health, but always controversial
  - Disturbing the natural order
  - Safety and untoward effects
  - Public good versus individual rights
  - Uneven access
  - ...

# The paradox of vaccines



# Vaccines

- Many ethical challenges:
  - Development and testing of vaccines
  - Distribution/allocation of vaccines
  - Public health use of vaccines
  - Social acceptability of vaccines
  - Vaccine related injury and compensation
  - Anti- vax movement
  - Etc.



# Vaccines

- Many ethical challenges:
  - Development and testing of vaccines
  - Distribution of vaccines
  - Public health use of vaccines
  - Untoward effects
  - Social acceptability of vaccines
  - Allocation
  - Etc.





# Vaccine development and testing

- **Basic research**
- **Preclinical testing**
- **Clinical Testing**
  - Phase I - Safety/toxicity
  - Phase II- Safety/immunogenicity
  - Phase III- Safety/efficacy
  - Phase IV- Post-marketing



Before a new vaccine is ever given to people, extensive lab testing is done that can take several years. Once testing in people begins, it can take several more years before clinical studies are complete and the vaccine is licensed.

# How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

## PHASE 1

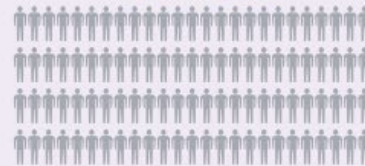


**20-100  
healthy volunteers**



- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

## PHASE 2



**several hundred  
volunteers**

- What are the most common short-term side effects?
- How are the volunteers' immune systems responding to the vaccine?

## PHASE 3



**hundreds or thousands  
of volunteers**

- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

**FDA licenses the vaccine only if:**

- It's safe and effective
- Benefits outweigh risks

Vaccines are made in batches called lots.



Manufacturers must test all lots to make sure they are safe, pure and potent. The lots can only be released once FDA reviews their safety and quality.

The FDA inspects manufacturing facilities regularly to ensure quality and safety.



**FOR MORE INFORMATION, VISIT [HTTPS://WWW.FDA.GOV/CBER](https://www.fda.gov/cber)**

[https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine.html?CDC\\_AA\\_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fparents%2Finfographics%2Fjourney-of-child-vaccine-text.html](https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fparents%2Finfographics%2Fjourney-of-child-vaccine-text.html)

# Vaccine Development Goals

- **SAFE-** Reasonably/acceptably safe in a wide range of possible users
- **EFFECTIVE** in a large percentage of persons who are at risk
- Relatively simple to deliver, store, and administer
- Affordable & Widely available
- Used

# Ethical challenges in phase 3 vaccine research

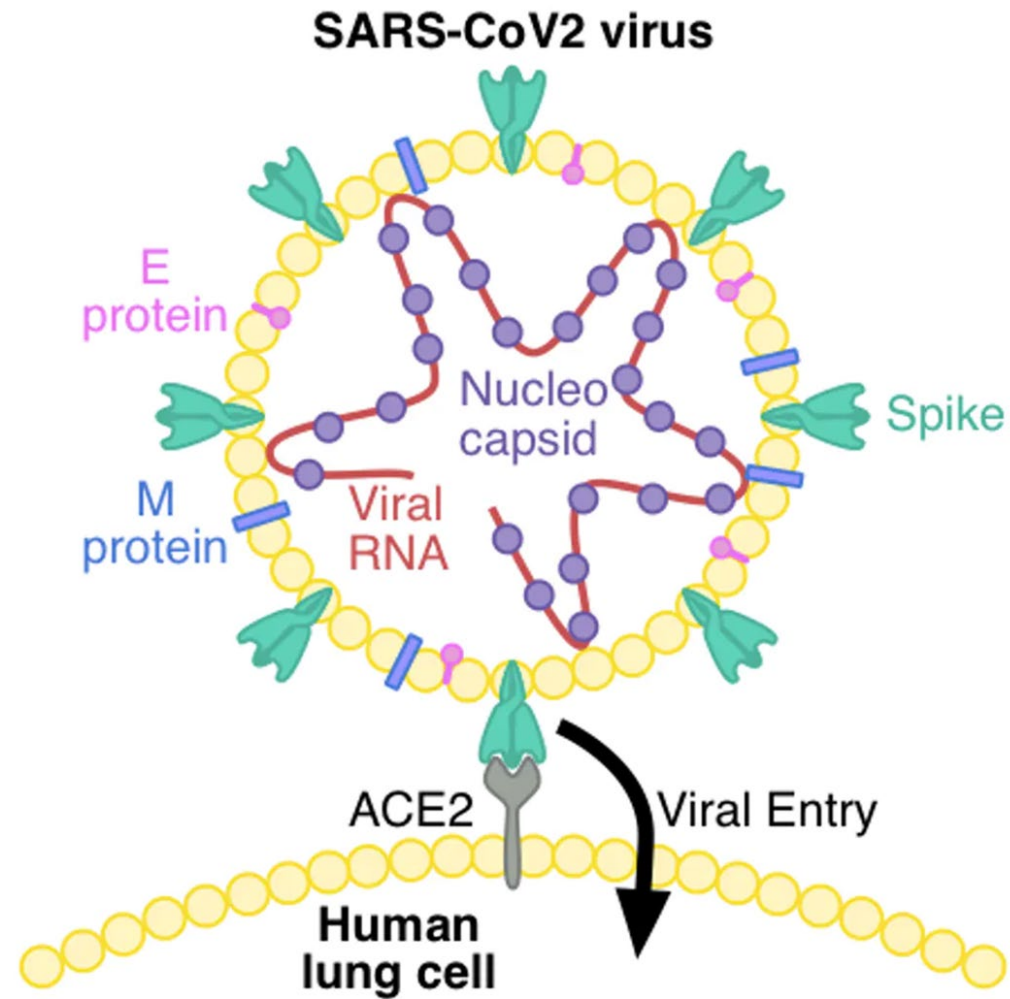
- Healthy populations (at risk of infection or of disease)
- Large numbers of participants
- Some risk to individuals, conditional individual benefit
- Benefit to community or society



# Vaccine benefits to community and society

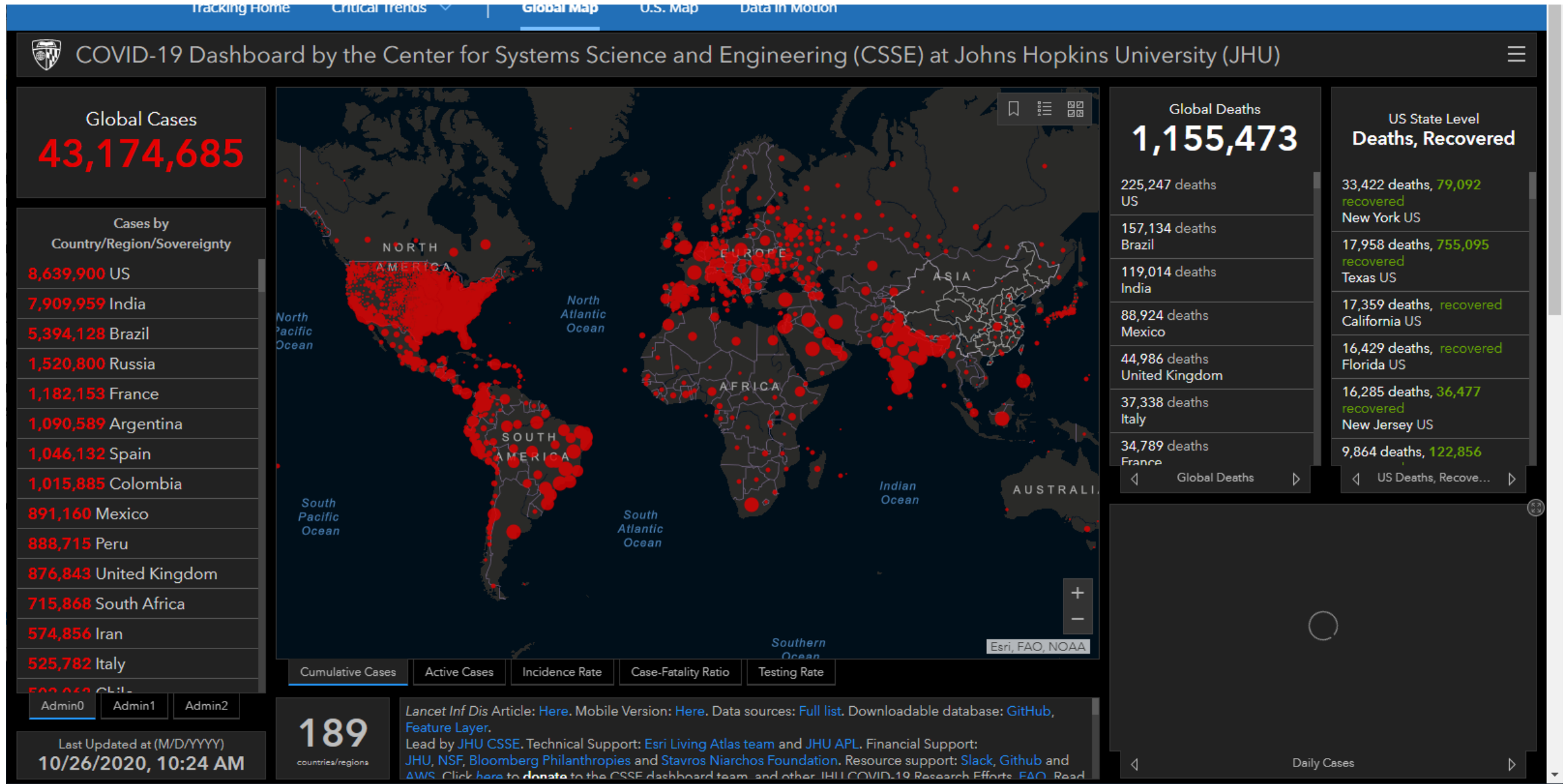
- Reduced morbidity and mortality
- Herd immunity and protection
  - Herd immunity occurs when the % of persons immune to a disease (the herd) is large enough to reduce the likely spread from person to person. Others in the community, not just those who are immune, are protected.
  - Can protect those who can't receive or sufficiently respond to a vaccine.

# SARS CoV-2



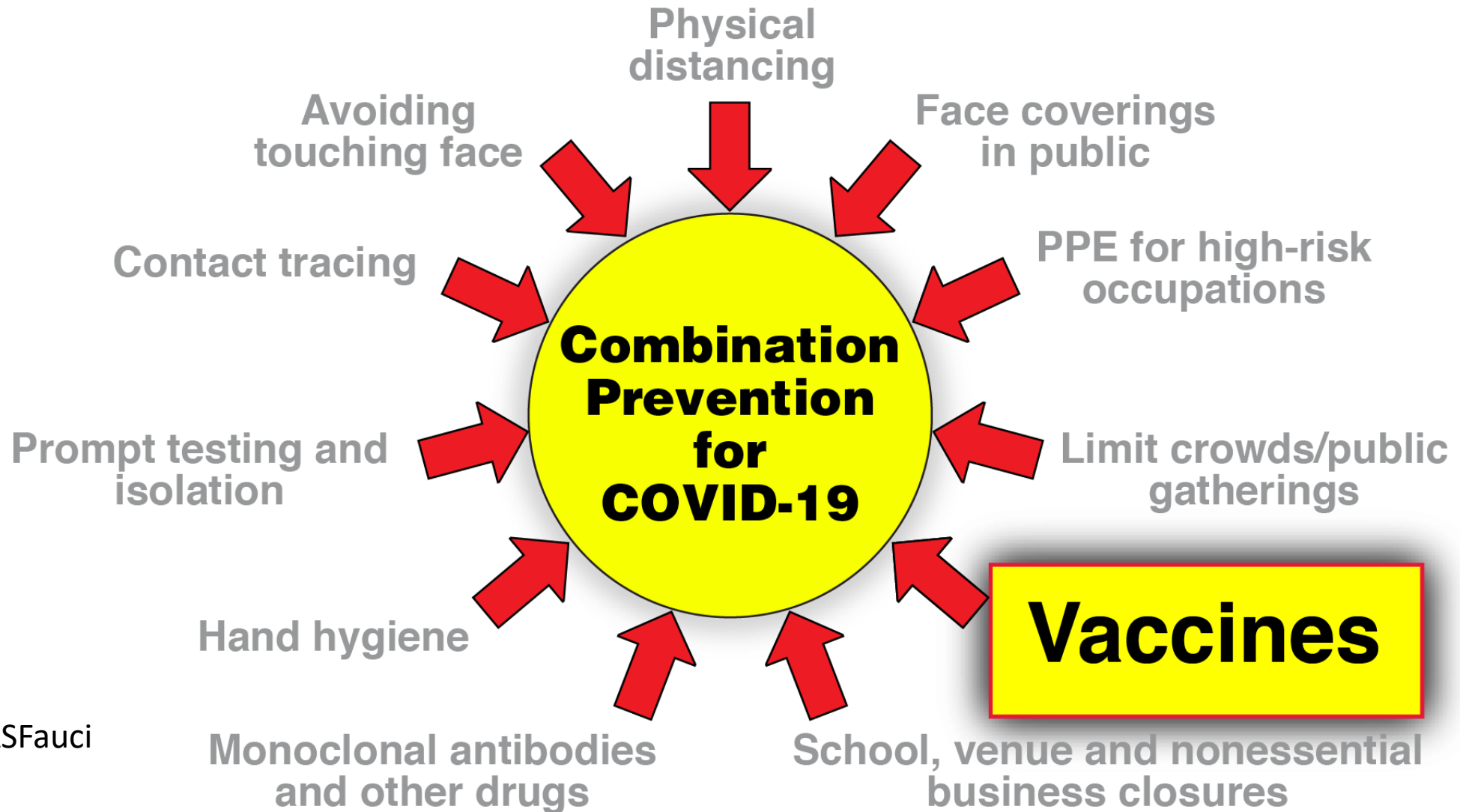


# SARS CoV-2



# **Prevention of COVID-19 with a Highly Effective Vaccine and Widespread Uptake**

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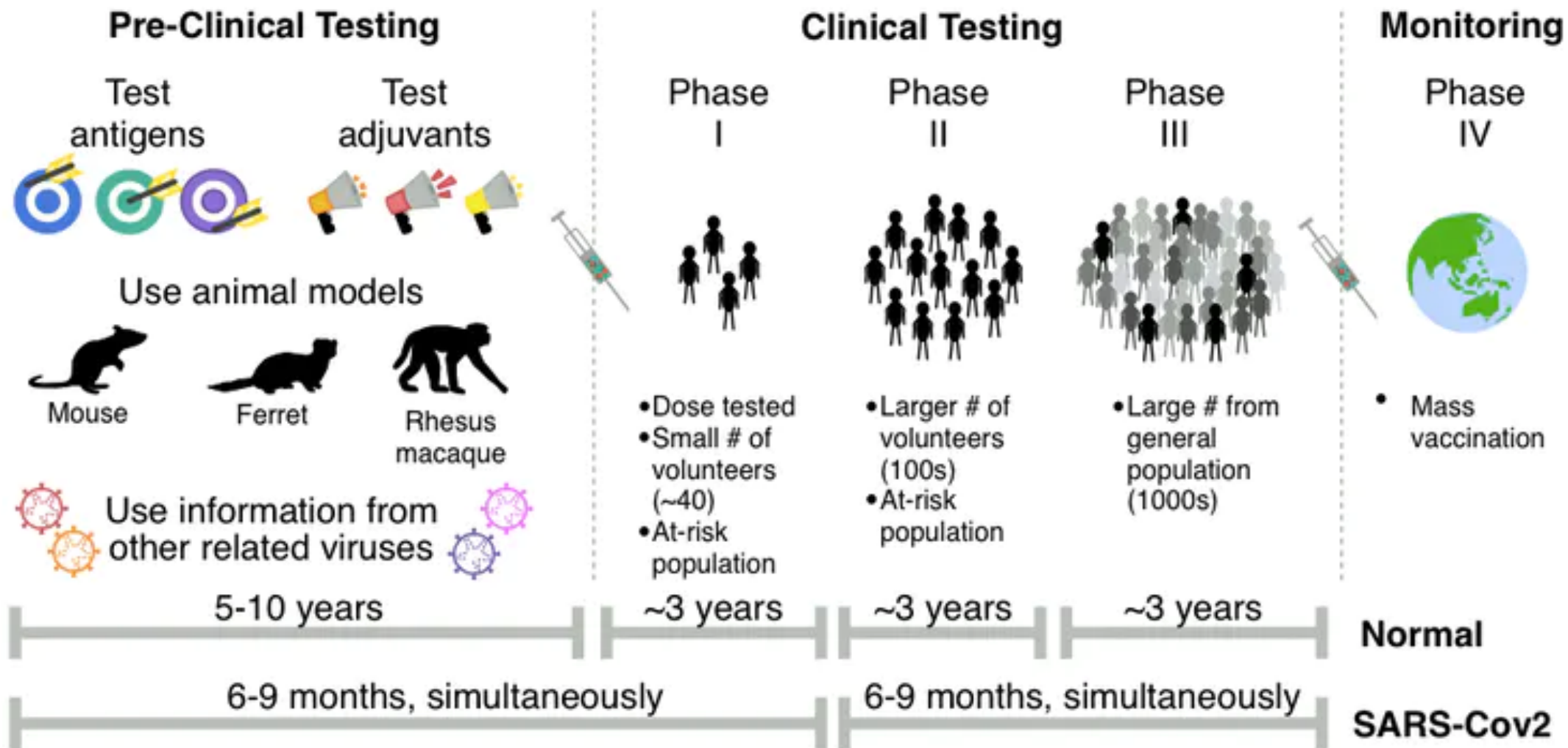


Courtesy of ASFauci



# COVID-19 Vaccine Development Goals

- **SAFE**- Reasonably/acceptably safe in a wide range of possible users
- **EFFECTIVE** in a large percentage of persons who are at risk
- Relatively simple to deliver, store, and administer
- Affordable & Widely available
- Used
- **FAST**



# Accelerating SARS CoV-2 vaccines

- “Pandemic” Speed (Coalition for Epidemic Preparedness Innovation- CEPI)
- Operation Warp Speed- (US govt)
  - Produce and deliver 300 million doses of safe and effective vaccines as early as Jan 2021; part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics.
  - Partnership among DHHS components, including CDC, NIH, BARDA, ASPR, DoD, and engagement with private firms and other federal agencies
  - Select promising candidates, investing in development and manufacturing.
  - Distribution strategy

# Pace of vaccine development

- Vaccine research started within weeks of identifying and sequencing SARS CoV-2
- By October 2020, 200 vaccine candidates in the pipeline
- “Shortcuts in vaccine development and testing might expedite the timeline of scientific progress, *and* could also result in compromising quality, acceptability, and ethics”

Grady C et al. So much at stake: Ethical tradeoffs in accelerating SARS CoV-2 vaccine. *Vaccine* Aug 2020

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# The Risks of Rushing a COVID-19 Vaccine

Telescoping testing time lines and approvals may expose all of us to unnecessary dangers

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By William A. Haseltine on June 22, 2020

VIEWPOINT

COVID-19: BEYOND TOMORROW

## Adverse Consequences of Rushing a SARS-CoV-2 Vaccine Implications for Public Trust

**Brit Trogen, MD, MS**  
NYU Langone Health,  
New York, New York.

**David Oshinsky, PhD**  
NYU Langone Health,  
New York, New York.

**Arthur Caplan, PhD**  
NYU Langone Health,  
New York, New York.



Viewpoint  
pages 2462, 2458,  
and 2455

As the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic persists across the US and the world, the spotlight on vaccine science has never been more intense. Researchers across the globe are working rapidly to produce a potential vaccine, and 7 candidates are already in clinical trials.<sup>1</sup> Operation Warp Speed, the vaccine development project announced by President Trump, has advocated for a vaccine to be made available in the US by the beginning of 2021.<sup>1</sup> But for scientists and physicians, the term “warp speed” should trigger concern. Good science requires rigor, discipline, and deliberate caution. Any medical therapy approved for public use in the absence of extensive safeguards has the potential to cause harm, not only for COVID-19 prevention efforts and vaccine recipients, but also for public trust in vaccination efforts worldwide.

Long before coronavirus disease 2019 (COVID-19), vaccine hesitancy and refusal were increasing.<sup>2</sup> In 2019, the World Health Organization listed vaccine refusal as one of the top 10 global health threats.<sup>3</sup> Pediatricians, in particular, frequently encounter resistance to childhood vaccinations, and as a result, outbreaks of measles

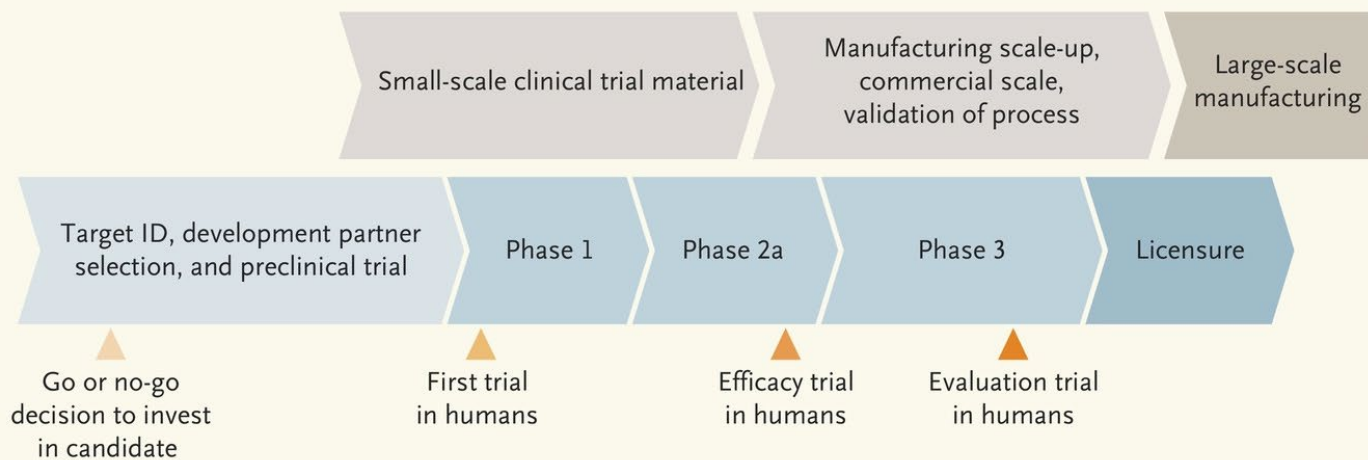
activated polio vaccine developed by Jonas Salk was declared “safe, potent, and effective” following the largest public health experiment in the nation’s history, involving more than a million schoolchildren.<sup>5</sup> Within weeks, however, the miracle vaccine intended to end the scourge of polio stood accused of causing it. Years in development, the Salk vaccine had been rigorously tested in preparation for the massive trials. But the very success of these trials led to an understandable outcry for the immediate, but premature, public release of the vaccine. Five pharmaceutical companies were given Salk’s formula and left to produce the vaccine without significant oversight. As speed took precedence over caution, serious mistakes went unreported.<sup>5</sup> One company, Cutter Laboratories, distributed a vaccine so contaminated with live poliovirus that 70 000 children who received that vaccine developed muscle weakness, 164 were permanently paralyzed, and 10 died.<sup>6</sup> Not surprisingly, that incident forced the federal government to directly intervene. The legacy of this event is a regulatory landscape in which vaccines undergo thousands of tests to ensure their safety and effectiveness.<sup>6</sup>

Yet on rare occasions, this vital evidence-based process of vaccine development and testing has still been ignored. In 1976, concerns about the emergence of a new swine flu strain reminiscent of the lethal 1918 version led President Gerald Ford to convene a panel that recommended a government-backed mass vaccination program.<sup>7</sup>

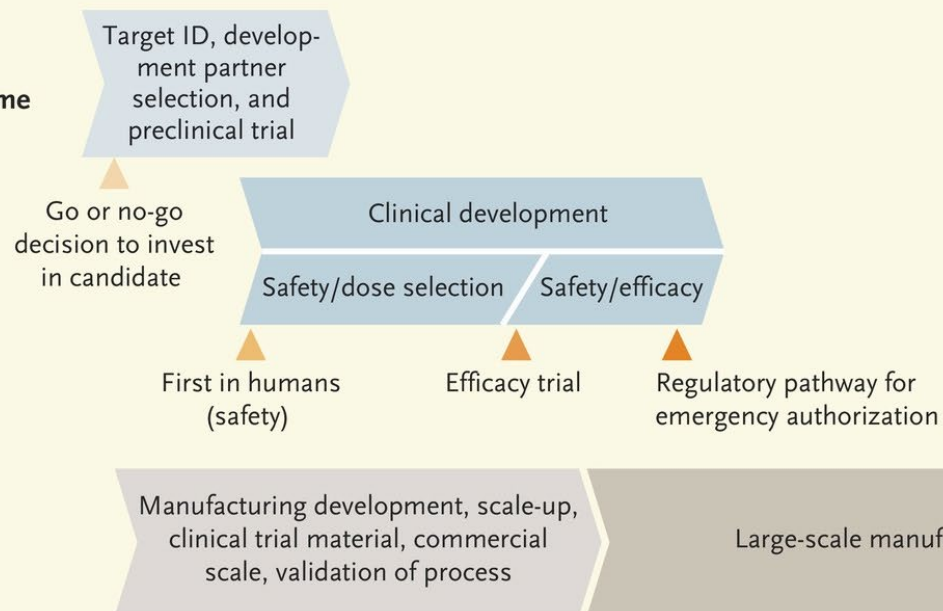
What cannot and must not be allowed  
is for desperation to result in the  
suspension of scientific principles  
and ethical research values.



**Traditional Paradigm —  
Multiple Years**



**Outbreak Paradigm —  
Overlapping Phases  
Shorten Development Time**



Access: Geographic spread of manufacturing and development sites and pursuit of emergency authorization before licensure

# Various approaches for testing SARS CoV-2 vaccine

- Randomized controlled trials
- Combined phases
- Variations on RCT design
- Controlled human infection studies
- Approval via an emergency use authorization



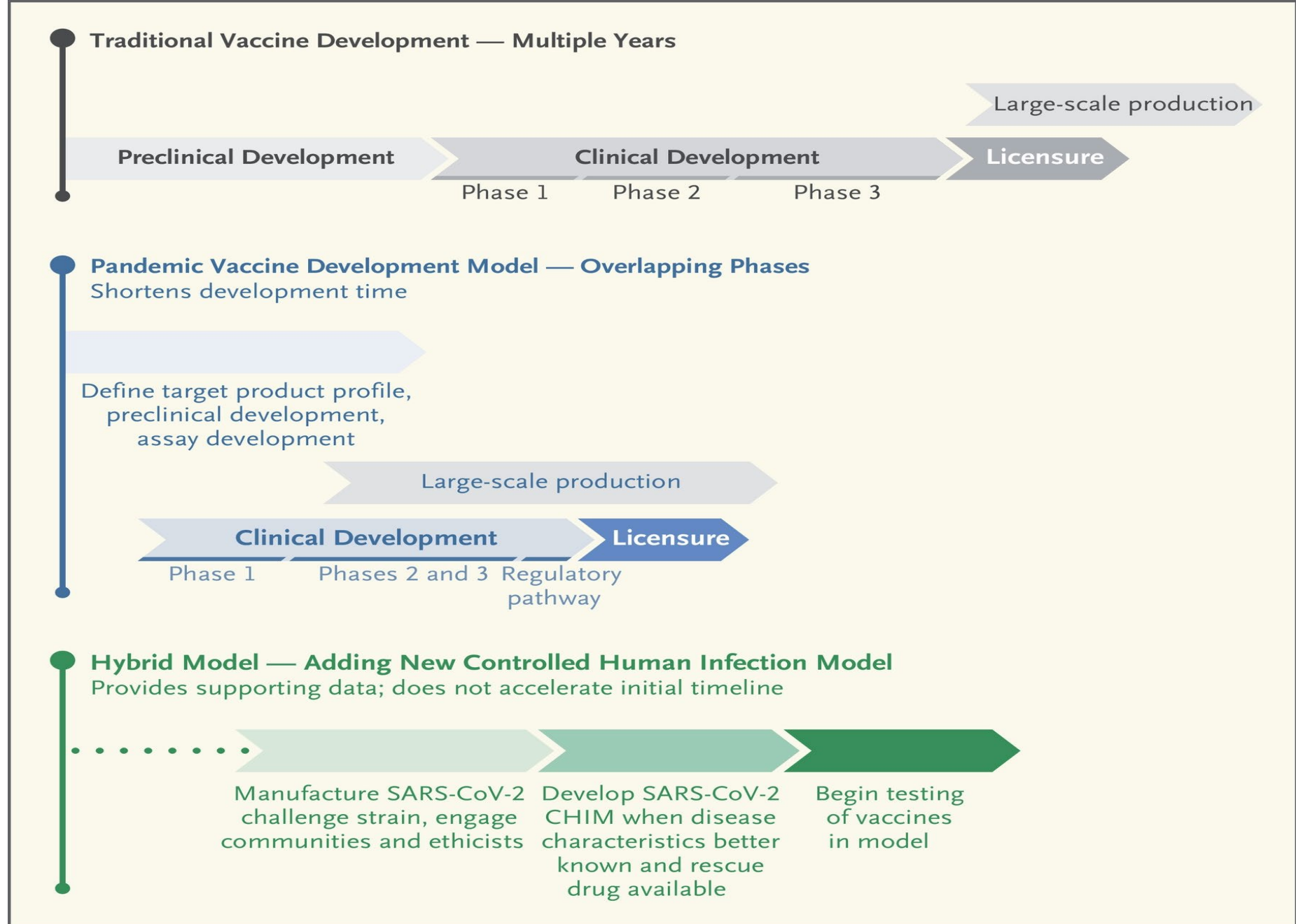
# Ethical framework: 8 principles

- Collaborative partnership
- **Valuable scientific question**
- **Valid scientific methodology**
- Fair subject selection
- **Favorable risk-benefit**
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel E, Wendler D, Grady C. What makes clinical research ethical? *J Am Med Assoc.* 2000; 283(20):2701-11; Chpt 11 Oxford Textbook 2008  
Emanuel E, Wendler D, Killen J, Grady C. *J Infect. Diseases* 2004; 189:930-7

**Table 1. Selected ethically relevant dimensions affecting social and scientific value in accelerated vaccine development approaches**

	Approach	Selected ethically relevant dimensions						
		Speed	Total number of research participants	Risks to participants and vaccinees	Cost	Feasibility - research capacity	Feasibility - pandemic dynamics	Social risks: Distrust or Negative Public Perception
<b>STANDARD</b>	<b>Consecutive Phase I, II and III Trials</b>	Years to trial completion	Thousands to tens of thousands	Low and carefully monitored	High	High: existing experience and infrastructure	Showing efficacy depends on sufficient incidence	Usually low; familiar trajectory
<b>ACCELERATED</b>	<i>Individually randomized RCT Combining Phases II/III</i>	↓	↓	↔	↓	↔	↔	↔ ↑
	<i>Cluster randomized RCT in Phase III</i>	↓	↓	↔	↓	↔ ↑	↔ ↓	↑
	<i>EUA following Phase I</i>	↓↓	N/A	↑ ↑	↓	N/A	N/A	↑ ↑
	<i>CHI study with or without field trial</i>	↓	↓↓	↑	↓	↑	↓	↑ ↑



Deming M et al. Accelerating Development of SARS-CoV-2 Vaccines — The Role for Controlled Human Infection Models. *NEJM* Sept 2020

# Vaccine RCT considerations

## Design:

- Parallel individual randomization
- Cluster randomization
- Alternative design- e.g. ring vaccination, stepped-wedged

Comparator

Randomization

Double Blinded

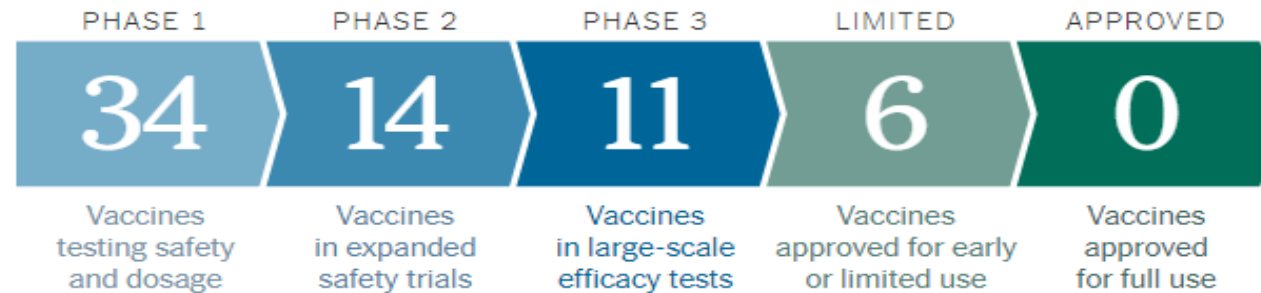
Sample size

Primary endpoints

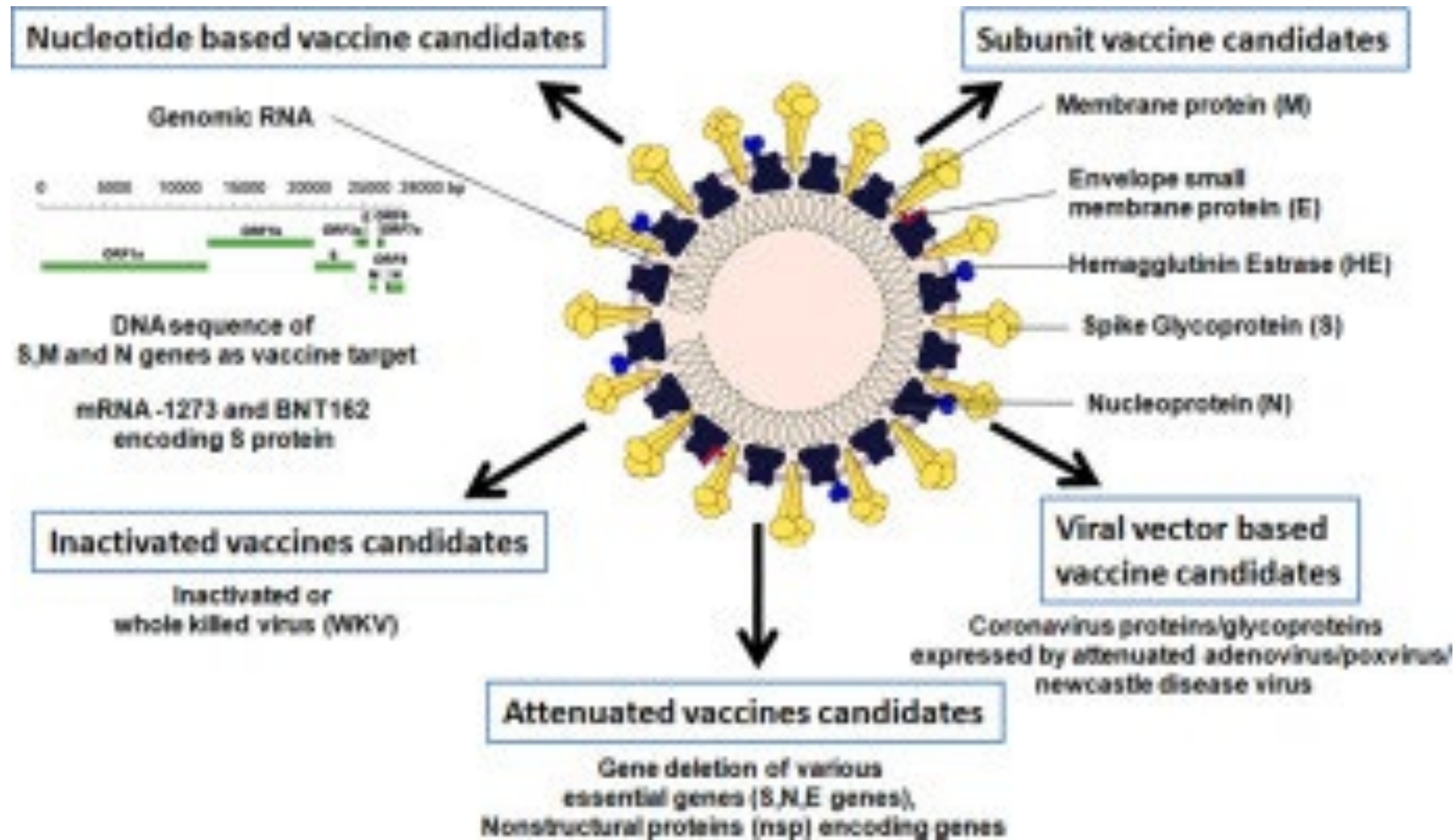
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# Coronavirus Vaccine Tracker

By Jonathan Corum, Sui-Lee Wee and Carl Zimmer Updated October 26, 2020










Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by [next year](#). Researchers are testing **48 vaccines** in clinical trials on humans, and at least 88 preclinical vaccines are [under active investigation](#) in animals.



Platforms used by previous vaccines: inactivated, live attenuated, subunit  
 Newer Platforms: Nucleotide based, viral vector based



# Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid		Enrolled	Ongoing
		Enrolled	Ongoing
Viral vector		Enrolled	Ongoing
		Enrolled	Ongoing
		Ongoing	--
Protein subunit		Ongoing	Ongoing
		Ongoing	--

	Pfizer	Moderna	Astra-Zeneca
Sample size	30,000	30,000	30,000
Participants getting vaccine	15,000	15,000	20,000
Efficacy target	60%	60%	50%
Lower 95% CI efficacy	30%	30%	30%
Number of Events at Completion	164	151	150
Number of Interim Analyses	4	2	1
Alpha-spending function at Interim Analysis for Stopping Rule	Pocock-type	O'Brien-Fleming type	Lan-DeMets
Number of Events at 1 <sup>st</sup> (or only) Interim Analysis	32	53	75



# FDA guidance

- US FDA. *Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry*, June 2020.  
<https://www.fda.gov/media/139638/download>
- US FDA. *Emergency Use Authorization for Vaccines to Prevent COVID-19: Guidance for Industry*, October 2020.  
<https://www.fda.gov/media/142749/download>

# COVID-19 Vaccine development

- Scientific challenges
- Ethical challenges
- Practical challenges
- Societal challenges



# Public trust

- Science literacy
- Trust in science
- Public Trust



June 30, 2020

# Science

**Just 50% of  
Americans Plan to  
Get a COVID-19  
Vaccine.  
Here's How to Win  
Over the Rest**

W Cornwall

Courtesy AS Fauci

**Do you plan to get a coronavirus vaccine when one is available?**

Overall



Under age 60



Age 60 and older



White



Black



Hispanic



Yes Not sure No Did not answer

# Willingness to take vaccine

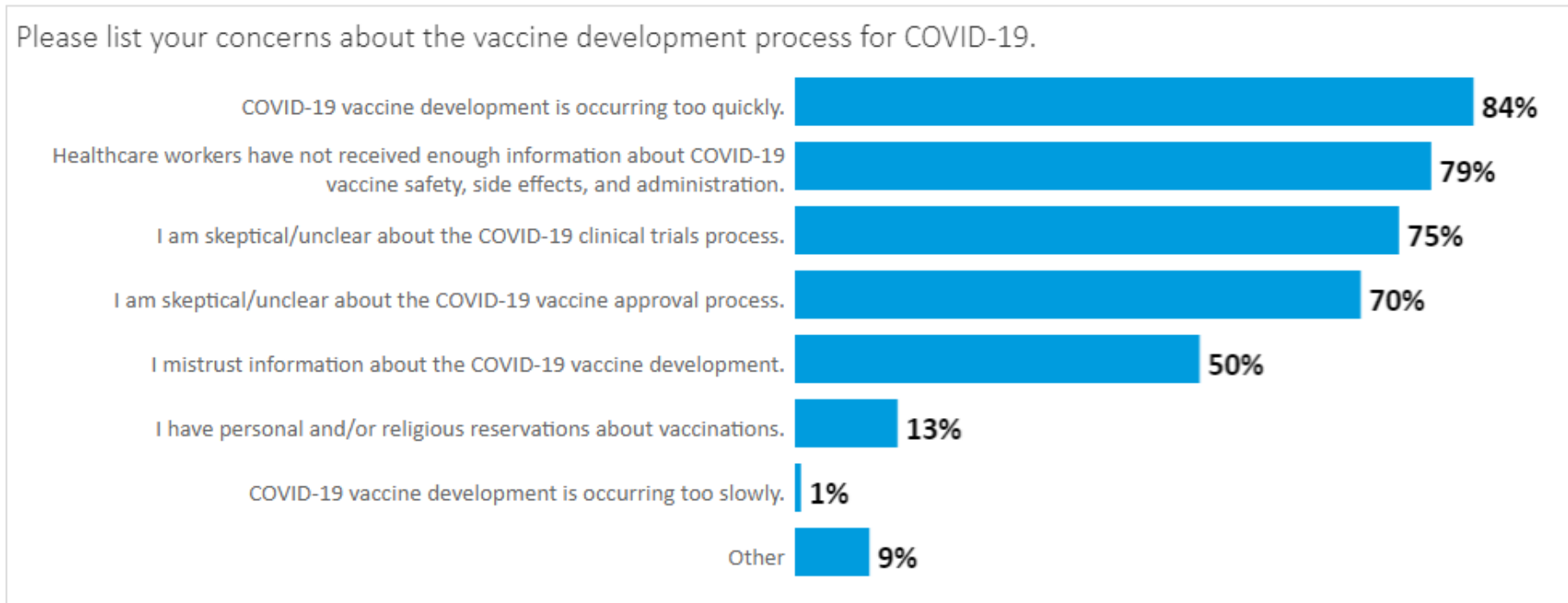
	Accept COVID Vaccine if available?	Accept vaccine if employer recommended?
Completely agree	46.8%	39.1
Somewhat agree	24.7%	29.5
Neutral	14.2 %	20.6
Somewhat disagree	6.1	8.1
Completely disagree	8.1	9.8

A study of potential acceptance of a COVID-19 vaccine in 13,426 randomly selected individuals across 19 countries, most with a high COVID-19 burden.

- High heterogeneity in responses between countries.
- Furthermore, willingness to get vaccinated might not be necessarily a good predictor of acceptance

Lazarus et al *Nature Med* Oct 2020

# More data



American Nurses Foundation, Pulse on the Nation's Nurses COVID-19 Survey Series: COVID-19 Vaccine, October 2020.  
(N=12,939 US nurses)

<https://www.nursingworld.org/practice-policy/work-environment/health-safety/disaster-preparedness/coronavirus/what-you-need-to-know/covid-19-vaccine-survey/>



COVID-19

# Scientists Warn Americans Are Expecting Too Much From a Vaccine

By [Liz Szabo](#) and [JoNel Aleccia](#)

OCTOBER 28, 2020

[REPUBLIC THIS STORY](#)[DISPONIBLE EN ESPAÑOL](#)

# Ethical framework: 8 principles

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- Valid scientific methodology
- Fair subject selection
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Emanuel E, Wendler D, Killen J, Grady C. *J Infect. Diseases* 2004; 189:930-7